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Papers

Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study

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Abstract

Objective To evaluate any association between obesity in middle age, measured by body mass index and skinfold thickness, and risk of dementia later in life.
Design Analysis of prospective data from a multiethnic population based cohort.
Setting Kaiser Permanente Northern California Medical Group, a healthcare delivery organisation.
Participants 10 276 men and women who underwent detailed health evaluations from 1964 to 1973 when they were aged 40-45 and who were still members of the health plan in 1994.
Main outcome measures Diagnosis of dementia from January 1994 to April 2003. Time to diagnosis was analysed with Cox proportional hazard models adjusted for age, sex, race, education, smoking, alcohol use, marital status, diabetes, hypertension, hyperlipidaemia, stroke, and ischaemic heart disease.
Results Dementia was diagnosed in 713 (6.9%) participants. Obese people (body mass index ≥30) had a 74% increased risk of dementia (hazard ratio 1.74, 95% confidence interval 1.34 to 2.26), while overweight people (body mass index 25.0-29.9) had a 35% greater risk of dementia (1.35, 1.14 to 1.60) compared with those of normal weight (body mass index 18.6-24.9). Compared with those in the lowest fifth, men and women in the highest fifth of the distribution of subscapular or tricep skinfold thickness had a 72% and 59% greater risk of dementia, respectively (1.72, 1.36 to 2.18, and 1.59, 1.24 to 2.04).
Conclusions Obesity in middle age increases the risk of future dementia independently of comorbid conditions.

Introduction

With the ageing of the population it is expected that the incidence of dementia will increase 400% in the next 20 years.[1] There has also been a large increase in obesity worldwide, which is currently of epidemic proportions in the United States.[2] Contrary to findings from cross sectional studies,[3] a recent prospective study found that obesity in elderly woman increases the risk of dementia.[4]

Assessment of obesity before old age may be a more accurate representation of adiposity as the ratio of lean to fat mass changes with ageing,[5] resulting in a decreased body mass index. The subclinical phase and initial onset of dementia affects appetite and causes weight loss,[3–7] skewing the temporal association between weight and dementia. Thus, one study found that weight loss precedes onset of dementia in elderly adults.[8] Obtaining weight measurements many years before the onset of dementia, as well as other measures of adiposity, would provide stronger evidence of causality between obesity and increased risk of dementia. For example, skinfold thickness, another marker of obesity associated with several diseases,[9 10] has not been examined in relation to dementia.

We determined the predictive value of mid-life adiposity, including body mass index and tricep and subscapular skinfold thickness, on the risk of developing dementia in a large multiethnic cohort of men and women followed for an average of 27 years.

Methods

Study population

We conducted a prospective analysis of 10 276 members of the Kaiser Permanente medical care programme of northern California who participated in voluntary periodic multiphasic health checks in San Francisco and Oakland, California, between 1964 and 1973. We identified participants aged 40-45 at the time of the multiphasic exam who were still members of Kaiser Permanente when outpatient diagnoses of dementia were available in 1994 (n=25 290). After we excluded those who had died before 1994 (n=2598), were no longer members (n=10 407), and had missing information on sex (n=9), 10 276 remained for analysis.

Kaiser Permanente is a non-profit, group practice integrated healthcare delivery system that includes hospitals and outpatient clinics that contract exclusively with a single group of physicians to provide all healthcare services to all members of the system. It covers more than a quarter of the population in the areas served, and members are representative of the sociodemographics of the local population in the service areas.[11]

Data collection and mid-life adiposity

At the multiphasic exam, participants were interviewed, underwent a clinical examination, and gave a blood sample. Information was collected on demographics and medical history. Full details have been published elsewhere.[12–14] Height and weight were measured according to standardised procedures.[12] We categorised body mass index (weight/height^2) as obese (≥30), overweight (25.0-29.9), normal (18.6-24.9), and underweight (≤18.5). Subscapular and triceps skinfold thickness were measured by trained technicians using Lange skinfold callipers (Cambridge Scientific Industries, Cambridge, MA) according to the criteria of the committee on nutritional anthropometry.[15 16]

P+ *A further table on age and body mass index can be found on bmj.com*

Diagnosis of dementia and other illnesses in later life

We searched the databases of inpatient and outpatient medical records from the care programme (from January 1994 to April 2003) for diagnoses of dementia and other illnesses. All cause dementia diagnoses included: dementia, Alzheimer's disease, and vascular dementia (ICD-9 (international classification of diseases, ninth revision) codes of 2900.0, 7809.3, 3310.0, 2904.1, 2900.1), and the criteria for these diagnoses did not change during the ascertainment period. We determined incidence of ischaemic heart disease, hypertension, stroke, hyperlipidaemia, and diabetes. To gather information on mortality we used the California automated mortality linkage system, which has a sensitivity of 97% compared with the National Death Index,[17] up to the end of 2000 and a matching linkage system, incorporating social security number, name, and address, from 2001 through the end of 2002. Mortality information was not available from January to April 2003.

Statistical analysis

We used SAS version 8.0 (SAS Institute, Cary, NC) for analyses. We used the log rank test to assess the association between time to diagnosis of dementia and characteristics measured at the multiphasic exam and Cox proportional hazard models to identify independent predictors of risk of late life dementia. Person years were calculated from onset of follow-up (1 January 1994) until onset of dementia or the earliest of death, end of Kaiser Permanente membership, or end of study (3 April 2003). We carried out χ^2 analyses to determine if there were any significant differences in the mid-life measures of adiposity and covariates by health plan membership status in 1994. Because measures of skinfold thickness varied significantly by sex ($P<0.0001$) we divided the distribution into fifths for men and women and used these in the analyses. For the body mass index models, the reference group was participants with a normal body mass index, while for skinfolds, it was those in the lowest fifth.

We generated three models for each measure of adiposity (body mass index and subscapular and triceps skinfolds): firstly, a model adjusted for age in mid-life (age at time of multiphasic exam) and education; secondly, a model additionally adjusted for age at start of ascertainment of dementia (age in 1994), race, sex (with the exception of sex stratified models), smoking, alcohol use, and martial status; and, thirdly, a model additionally adjusted for mid-life comorbidity (high total cholesterol, diabetes, and hypertension) and late life comorbidity (diabetes, ischaemic heart disease, stroke, hypertension, and hyperlipidaemia).

Table 1 Demographic characteristics of the participants at mid-life by dementia status. Figures are numbers (percentage) of participants unless stated otherwise*

	No dementia (n=9563)	Dementia (n=713)	P value†
Mean (SD) age at multiphasic exam (years)	42.45 (1.71)	42.89 (1.66)	<0.0001
Women	5168 (54.0)	396 (55.5)	0.8930
Men	4395 (46.9)	317 (44.5)	
Race:			
White	6864 (71.8)	489 (68.6)	0.0006
Black	1591 (16.6)	155 (21.7)	
Asian	636 (6.7)	36 (5.1)	
Other	471 (4.9)	33 (4.6)	
Level of education completed:			
Grade school (to age 12)	1159 (13.8)	129 (19.5)	<0.0001
High school (to age 18)	2895 (34.4)	214 (32.3)	
Trade or technical school	595 (7.1)	42 (6.3)	
College or university	3777 (44.8)	278 (41.9)	
Marital status:			
Married	7994 (84.5)	573 (81.5)	0.0451
Never married	489 (5.2)	38 (5.4)	
Divorced/widowed/ separated	972 (10.3)	92 (13.1)	
Smoking:			
Yes	5002 (58.6)	408 (60.4)	0.0627
No	3539 (41.4)	268 (39.6)	
Alcohol use:			
≤2 per week	5745 (60.4)	406 (57.1)	0.0732
3-5 per week	774 (8.1)	55 (7.7)	
≥6 per week	204 (2.1)	20 (2.8)	
Current/unknown quantity	681 (7.2)	63 (8.9)	
Past drinker	132 (1.4)	6 (0.8)	
Never drinker	1977 (20.8)	161 (22.6)	

*Missing data: education for 1185, marital status for 118, smoking for 1059, alcohol use for 52.
†P values were calculated with log rank test.

Results

From 1 January 1994 through 3 April 2003, 713 participants were diagnosed with dementia (table 1). Mean age at initial recorded diagnosis was 74.5 years (range 66-82). The mean time to start of ascertainment of dementia was 26.5 years after the multiphasic exam. Those with the diagnosis were more likely to be older, have a grade school education (completed schooling to age 12), and be unmarried in mid-life.

At mid-life, 10% of the cohort were obese, 36% overweight, 53% normal weight, and 1.3% underweight. The prevalence of a subsequent diagnosis of dementia was significantly higher for those who were obese or overweight at mid-life (table 2). Those in the highest fifth for subscapular and tricep skinfold measurements at mid-life were more likely to have dementia than those in the lowest fifth (table 2). Post hoc analyses of the 10 276 participants in the study compared with the 10 407 who were excluded because they were no longer health plan members in 1994 showed no significant differences in any of the mid-life measures of adiposity or covariates by status of health plan membership in 1994. We also conducted post hoc analyses to ensure that there was no selection effect due to age, indeed participants who were obese or overweight were not older at time of ascertainment of dementia than those of normal weight (see table on bmj.com). We checked the proportionality of hazards for each covariate by entering interaction terms of the covariate by person years into the model. The P values for each were non-significant ($P>0.06$), indicating all hazards were proportional.

Compared with those normal weight at mid-life, obese people had a 74% greater risk of dementia (hazard ratio 1.74, 95% confidence interval 1.34 to 2.26, fully adjusted model, table 3), while those who were overweight had a 35% greater risk (1.35, 1.14 to 1.60, fully adjusted model). In sex specific models body mass index was associated with dementia more strongly in women (body mass index*sex interaction term $P=0.06$). Obese women were twice as likely to have dementia as women of normal weight (2.07, 1.49 to 2.89, fully adjusted model), while obese men had a non-significant 30% increase in risk (1.30, 0.84 to 1.87, fully adjusted model). Overweight women were 55% more likely to have dementia than women of normal weight (1.55, 1.22 to 1.97, fully adjusted model), while overweight men had a non-significant 16% increase in risk compared with men of normal weight (1.16, 0.91 to 1.46, fully adjusted model). Being underweight was not significantly associated with dementia in either sex, but only 0.6% of men and 1.9% of women had a body

Table 2 Mid-life adiposity of participants by dementia status. Figures are numbers (percentage) of participants

	No dementia (n=9563)	Dementia (n=713)	P value*
Body mass index†:			
Obese	942 (9.9)	87 (12.2)	0.0119
Overweight	3405 (35.6)	267 (37.5)	
Normal	5091 (53.2)	348 (48.8)	
Underweight	125 (1.3)	11 (1.5)	
Men:			
Total	4395	317	0.2531
Obese	432 (9.8)	38 (12.0)	
Overweight	2114 (48.1)	157 (49.5)	
Normal	1821 (41.4)	121 (38.2)	
Underweight	28 (0.6)	1 (0.3)	
Women:			
Total	5168	396	0.0392
Obese	510 (9.9)	49 (12.4)	
Overweight	1291 (25.0)	110 (27.8)	
Normal	3270 (63.3)	227 (57.3)	
Underweight	97 (1.9)	10 (2.5)	
Skinfolds (fifths):			
Subscapular:			
1	2175 (22.7)	140 (19.6)	<0.0001
2	1889 (19.8)	127 (17.8)	
3	1736 (18.2)	112 (15.7)	
4	1956 (20.5)	152 (21.2)	
5	1807 (18.9)	182 (25.5)	
Tricep:			
1	2012 (21.0)	127 (17.8)	0.0158
2	2033 (21.3)	148 (20.8)	
3	1810 (18.9)	122 (17.1)	
4	1980 (20.7)	161 (22.6)	
5	1728 (18.1)	155 (21.7)	

*P values calculated with log rank test.
†Obese (≥30), overweight (25.0-29.9), normal (18.5-24.9), underweight (<18.5); reference group is those with normal body mass index.

mass index <18.5, limiting the power to detect such an association. There were no significant race interactions in the association between body mass index and risk of dementia (P>0.15 for race*body mass index interaction term).

Measures of skinfold thickness at mid-life were significantly associated with risk of dementia at a magnitude similar to body mass index (table 4). Those in the highest fifth of subscapular skinfold had a 72% increased risk, while those in the highest fifth of tricep skinfolds had a 59% increased risk compared with those in the lowest fifth (fully adjusted models: 1.72, 1.36 to 2.18, and 1.59, 1.24 to 2.04, respectively). There was a non-significant trend for the effect of high subscapular skinfold thickness on risk of dementia to be stronger among men. Compared with those in the lowest fifth, men in the highest fifth of subscapular skinfold thickness had nearly a twofold increase in risk of dementia, while women had a 50% increase (table 4). Addition of body mass index to the skinfold models did not attenuate the effect (data not shown). Results did not vary by race in the association between skinfolds and dementia risk (P>0.15, interaction term skinfold measures*race).

Table 3 Cox proportional hazards model of body mass index at mid-life and risk of dementia. Figures are hazard ratios (95% confidence intervals)

Body mass index*	Adjusted for age at mid-life exam and education	Also adjusted for age at diagnosis, race, marital status, sex	Also adjusted for mid-life and late life comorbidity†
All			
Obese	1.38 (1.10 to 1.72)	1.56 (1.24 to 1.96)	1.74 (1.34 to 2.26)
Overweight	1.16 (1.01 to 1.34)	1.22 (1.04 to 1.42)	1.35 (1.14 to 1.60)
Underweight	1.41 (0.82 to 2.39)	1.46 (0.84 to 2.54)	1.24 (0.70 to 2.21)
Women			
Obese	1.59 (1.21 to 2.08)	1.80 (1.35 to 2.39)	2.07 (1.49 to 2.89)
Overweight	1.34 (1.09 to 1.63)	1.36 (1.10 to 1.68)	1.55 (1.22 to 1.97)
Underweight	1.63 (0.93 to 2.84)	1.73 (0.97 to 3.08)	1.45 (0.79 to 2.67)
Men			
Obese	1.08 (0.74 to 1.58)	1.22 (0.83 to 1.79)	1.30 (0.84 to 1.87)
Overweight	1.01 (0.82 to 1.25)	1.07 (0.86 to 1.33)	1.16 (0.91 to 1.46)
Underweight	0.55 (0.07 to 3.92)	0.55 (0.08 to 3.96)	0.53 (0.07 to 3.82)

*Obese (≥30), overweight (25.0-29.9), normal (18.5-24.9), underweight (<18.5); reference group is those with normal body mass index.
†Mid-life comorbidity includes hypertension, diabetes, and high cholesterol; late life comorbidity includes hypertension, stroke, diabetes, ischaemic heart disease, and hyperlipidaemia.

Table 4 Cox proportional hazards model of skinfold thickness (according to fifth of distribution*) at mid-life and risk of dementia. Figures are hazard ratios (95% confidence intervals)

Skinfold thickness	Adjusted for age at mid-life exam and education	Also adjusted for age at diagnosis, race, marital status, and sex	Also adjusted for mid-life and late life comorbidity†
Subscapular			
All:			
2nd fifth	1.09 (0.80 to 1.31)	1.02 (0.80 to 1.31)	1.05 (0.82 to 1.34)
3rd	0.95 (0.73 to 1.23)	0.96 (0.74 to 1.25)	1.03 (0.79 to 1.34)
4th	1.17 (0.93 to 1.49)	1.16 (0.91to1.47)	1.25 (0.98 to 1.59)
Highest	1.57 (1.25 to 1.97)	1.54 (1.23 to 1.94)	1.72 (1.36 to 2.18)
Women:			
2nd	0.83 (0.60 to 1.16)	0.84 (0.60 to 1.17)	0.85 (0.61 to 1.18)
3rd	0.79 (0.56 to 0.11)	0.80 (0.57 to 1.13)	0.86 (0.61 to 1.22)
4th	1.04 (0.76 to 0.42)	1.02 (0.74 to 1.39)	1.09 (0.79 to 1.50)
Highest	1.38 (1.02 to 1.86)	1.39 (1.03 to 1.88)	1.52 (1.11 to 2.08)
Men:			
2nd	1.32 (0.90 to 1.92)	1.33 (0.91 to 1.94)	1.37 (0.94 to 2.02)
3rd	1.21 (0.81 to 1.80)	1.21 (0.81 to 1.82)	1.30 (0.87 to 1.95)
4th	1.36 (0.94 to 1.97)	1.37 (0.95 to 1.98)	1.48 (1.02 to 2.14)
Highest	1.83 (1.29 to 2.61)	1.75 (1.22 to 2.50)	1.97 (1.36 to 2.85)
Triceps			
All:			
2nd	1.14 (0.88 to 1.46)	1.18 (0.92 to 1.52)	1.20 (0.84 to 1.54)
3rd	1.10 (0.85 to 1.42)	1.12 (0.87 to 1.45)	1.13 (0.87 to 1.46)
4th	1.31 (1.03 to 1.67)	1.34 (1.06 to 1.71)	1.42 (1.11 to 1.82)
Highest	1.47 (1.15 to 1.87)	1.49 (1.17 to 1.90)	1.59 (1.24 to 2.04)
Women:			
2nd	0.98 (0.70 to 1.37)	1.04 (0.75 to 1.46)	1.08 (0.77 to 1.51)
3rd	1.01 (0.72 to 1.41)	1.06 (0.75 to 1.49)	1.05 (0.75 to 1.47)
4th	1.13 (0.82 to 1.56)	1.16 (0.84 to 1.60)	1.26 (0.91 to 1.74)
Highest	1.38 (1.01 to 1.89)	1.43 (1.04 to 1.97)	1.53 (1.10 to 2.12)
Men:			
2nd	1.35 (0.92 to 1.96)	1.37 (0.94 to 0.99)	1.35 (0.93 to 1.98)
3rd	1.23 (0.82 to 1.83)	1.18 (0.79 to 1.78)	1.21 (0.80 to 1.82)
4th	1.56 (1.08 to 2.26)	1.59 (1.10 to 2.31)	1.63 (1.12 to 2.37)
Highest	1.20 (1.06 to 2.26)	1.52 (1.04 to 2.22)	1.62 (1.11 to 2.38)

*Reference groups are those in lowest fifth.
†Mid-life comorbidity includes hypertension, diabetes, and high cholesterol; late life comorbidity includes hypertension, stroke, diabetes, ischaemic heart disease, and hyperlipidaemia.

Discussion

Adiposity in mid-life is associated with an increased risk of dementia in old age independent of sociodemographic characteristics and common comorbidities. Obesity and overweight in middle age as measured by body mass index and skinfold thickness were strongly associated with risk of dementia in later life. To date, this is the first study to determine the contribution of mid-life adiposity and skinfold thickness on risk of dementia.

Strengths and weaknesses of study

Strengths of the study include the longitudinal design with skinfold measures from two parts of the body as well as body mass index, the long follow-up, the breadth of information on other diseases in middle and old age, and the well characterised representative sample with equal access to medical care. The participants were middle aged when risk factors were assessed, thus subclinical dementia at baseline is highly unlikely.

This study also has limitations. We could assess dementia status only among participants who were still members of the health plan when dementia was diagnosed. However, there were no differences in adiposity or sociodemographic characteristics in those who didn't continue in the health plan. Information on weight cycling, dieting, nutrition, or mid-life measures of cognitive functioning were not collected, and other studies have shown that several different nutritional factors are associated with dementia.[18 19] A measure of central obesity, such as waist circumference would have been informative, but this was not collected. As diagnoses of dementia were made during medical visits, some cases of dementia may have been missed in those who did not participate in visits. This, however, would bias results in an underestimation of the effects of obesity on dementia.

Mechanisms of effects

One plausible reason for an increased risk of dementia with adiposity is through cardiovascular disease and diabetes as both these conditions increase the risk of dementia.[14 20–22] Yet, adjustment for prevalence of diabetes and cardiovascular disease at mid-life and later did not attenuate the associations. Adiposity is also one component of the metabolic syndrome, which has also been shown to cause cognitive decline, particularly in those with high levels of inflammation.[23]

Perhaps adiposity has a direct effect on neuronal degradation. Genetically obese, leptin receptor deficient rodents have impaired performance on spatial memory tasks[24] and long term potentiation of neurons in the hippocampus.[25] C reactive protein, an inflammatory marker, is increased in those with greater adiposity[26] and is associated with dementia[27] and cognitive decline.[23 28] Recently, obesity in elderly women was shown to be associated with greater cerebral atrophy[29] and white matter hyperintensity.[30] Future studies of cytokines produced in fat cells and neuronal functioning should be useful.

This is the first study to assess skinfold thickness on risk of dementia. Another study found that high skinfold thickness in mid-life was associated with Parkinson's disease.[31] Perhaps adiposity works together with other risk factors to increase neurodegenerative disease.

Body mass index predicted dementia more strongly among women. These findings, however, are consistent with the only published prospective study on body mass index and dementia.[4] There could be several reasons for this. There were fewer obese and overweight men, thus the power to detect an effect was reduced. Current body mass index categories may be insensitive indicators of adiposity in men because of less variation in the distribution of visceral fat.[5] Perhaps body mass index and risk of dementia in women is mediated through central obesity,[32] which is highly associated with insulin resistance,[33] cardiovascular disease,[32] increased adipocytokines,[34 35] and inflammatory markers.[36] All of these conditions could contribute to dementia. In the present study diabetes and cardiovascular disease did not attenuate the effect, though the role of central obesity, inflammation, and adipocytokines on our findings is unknown.

What is already known on this topic

A recent study found that high body mass index in old age is associated with an increased risk of dementia in women, though body mass index is an insensitive measure of adiposity in elderly people and the subclinical phase of dementia causes weight loss

No studies have prospectively evaluated the effect of obesity in middle age on the subsequent risk of future dementia, and no studies have determined whether skinfold thickness is associated with dementia

What this study adds

People who were obese in mid-life were 74% more likely to have dementia, while overweight people were 35% more likely to have dementia compared with those with normal weight

Increased adiposity in the subscapular and tricep region in middle age was associated with a 60-70% increase in risk of dementia

These findings were not attenuated by presence of comorbid diseases in mid and late life

Future directions

Future studies on obesity and dementia should consider distribution of adiposity and the role of adipocytokines on brain structure and function. If these results can be confirmed elsewhere, perhaps treatment of obesity might reduce the risk of dementia. Failure to contain the present epidemic of obesity may accentuate the expected age related increase in dementia.

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Amendment

This is version 2 of the paper. In this version, in the results section of the abstract the comparison is between men and women in the highest fifth (not the higher fifth) and the risk of dementia in men and women in the highest fifth of tricep skinfold thickness is 59% greater (not 60%), in table 1 the footnote says that data on education were missing for 1185 (not 185), and the adjusted hazard ratio for obese men is 1.30 (95% confidence interval 0.84 to 1.87 (not 1.20) in table 3 and the third paragraph of results.